Complete Summary

GUIDELINE TITLE

Alemtuzumab in chronic lymphocytic leukemia: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Fraser G, Smith CA, Imrie K, Meyer R, Hematology Disease Site Group. Alemtuzumab in chronic lymphocytic leukemia: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jun 14. 32 p. (Evidence-based series; no. 6-16). [35 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic lymphocytic leukemia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate whether alemtuzumab is a beneficial treatment option, with respect to outcomes such as survival, response rate, response duration, time-to-progression, and quality of life, for patients with B-cell chronic lymphocytic leukemia (CLL)
- To evaluate what toxicities are associated with the use of alemtuzumab
- To evaluate which patients are more likely, or less likely, to benefit from treatment with alemtuzumab

TARGET POPULATION

Adult patients with chronic lymphocyte leukemia (CLL)

INTERVENTIONS AND PRACTICES CONSIDERED

Alemtuzumab monotherapy and in combination therapy

MAJOR OUTCOMES CONSIDERED

- Survival
- Response rate
- Response duration
- Time-to-progression
- Quality of life
- Toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A systematic search of the published literature identified all reports relating to the use of alemtuzumab for the treatment of patients with chronic lymphocytic

leukemia (CLL). The MEDLINE (1966 to July 2005), CINAHL (1982 to July 2005), Healthstar (1975 to July 2005), CANCERLIT (1975 to July 2005), PREMEDLINE (July 2005), Cochrane Controlled Trials Register (July 2005), and Cochrane Database of Systematic Reviews (July 2005) databases were searched according to the strategy shown in Appendix A in the original guideline document. In addition, abstracts from the American Society of Hematology (ASH) (1995-2004) and the American Society of Clinical Oncology (ASCO) (1995-2005) annual conference proceedings were searched. The search strategy included only studies published in English. Publications evaluating alemtuzumab in non-human subjects and those that were categorized as "published comments," "letters," and "editorials" were excluded. The United Kingdom Coordinating Committee on Cancer Research (UKCCCCR) Register, Physician Data Query (PDQ), National Institute of Health (NIH) Clinical Trials, and the European Organization for Research and Treatment of Cancer (EORTC) databases were searched to identify ongoing clinical trials. The National Guidelines Clearinghouse was searched for clinical practice guidelines. The references for each selected article were also reviewed. Where it was deemed necessary, the authors of included publications were contacted to obtain missing or additional data. It should be noted that a preliminary literature search was performed in November 2002 and subsequently updated in November 2004 and July 2005. After the preliminary literature search, the study selection criteria were amended to exclude studies with fewer than 20 evaluable patients. As a result, studies in the preliminary literature search that had fewer than 20 evaluable patients were later removed from the report. The data from those small studies, had they been included, would not have significantly affected the results or the Disease Site Group (DSG) recommendations. For the sake of clarity, results from the preliminary and updated searches for this systematic review are presented together.

Study Inclusion Criteria

Articles were selected for inclusion in this systematic review if they met the following criteria:

1. Studies included patients with chronic lymphocytic leukemia (CLL).
2. Studies tested the role of alemtuzumab as either induction or consolidation therapy, and either as a single agent or in combination with other therapy.
3. Results were reported for any of the following outcomes: survival, quality of life, time-to-progression, response duration, response rate, or adverse effects.
4. Trials had a minimum sample size of 20 evaluable patients.

Two independent observers reviewed the title and abstract of each citation. They were blinded to author name, institution, name of journal, nature of the paper (full paper or abstract), and results. The blinded observers scored each abstract as follows: "yes" if it met inclusion criteria, "no" if it did not meet inclusion criteria, or "maybe" if there was uncertainty. If both observers agreed that the abstract met the inclusion criteria, the complete document, if available, was retrieved for further analysis. In cases of disagreement, both observers reassessed the blinded abstracts together to achieve consensus. Where consensus could not be reached, or in cases where both observers gave a score of "maybe," the full document was retrieved and assessed by both reviewers to achieve

consensus regarding eligibility. The reasons for excluding retrieved articles were documented.

NUMBER OF SOURCE DOCUMENTS

Twenty-two publications were reviewed

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Due to a lack of adequately designed randomized controlled trials (RCTs) in the sample, a formal meta-analysis was deemed inappropriate. Where possible, response rates from single-arm studies evaluating similar patient groups were calculated. Data were pooled using intention-to-treat groups, and response proportions computed.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In its deliberations, the Hematology Disease Site Group (DSG) places particular emphasis on the following: (a) results from published randomized controlled trials (RCTs) (where available), (b) the recognition of a hierarchy of outcomes that should influence treatment decisions, with priority given to therapies found to extend life or improve quality of life, and (c) the potential toxicities associated with treatment, with particular emphasis on those toxicities seen in the patients most likely to make up the eventual population treated. The members of the Hematology DSG had considerable difficulty reaching consensus on the appropriate wording of the recommendation for a potential indication for alemtuzumab in patients with chronic lymphocytic leukemia (CLL); the recommendation went through multiple iterations (see section 3, Guideline Development and External Review—Methods and Results in the original guideline document). Based on their review of the evidence provided in this systematic review, the DSG considered several interpretations for the use of alemtuzumab in patients with CLL.

The DSG regards alemtuzumab as an active agent for the treatment of patients with relapsed or chemotherapy-refractory CLL. This conclusion is based on response data from single-arm studies that report partial responses in approximately one third of patients and recognizes that complete remissions are uncommon. From a perspective of drug and/or multi-agent regimen development, these data are extremely promising and warrant further testing of alemtuzumab.

In their deliberations, the DSG cited the following factors leading to the above recommendation: (a) a lack of data from properly designed RCTs, (b) a paucity of comparative data suggesting improved response duration, quality of life, or improved overall survival compared with alternative treatment approaches, and (c) significant potential toxicity, particularly infection-related morbidity and mortality. Given the anticipated toxicity, data from RCTs demonstrating improvement in clinically meaningful outcome measures (e.g., time-to-progression, quality of life, or overall survival) are required before recommendations permitting the routine use of alemtuzumab in this patient population can be made.

The practice guidelines published by European Society for Medical Oncology (ESMO) and the United Kingdom Chronic Lymphocytic Leukemia (UK CLL) Forum made recommendations regarding the use of alemtuzumab in previously treated patients. The ESMO guideline recommended alemtuzumab as an option for patients with refractory disease following first-line therapy, based on the lowest level evidence (American Society of Clinical Oncology [ASCO] level V evidence: small case-series). In addition, the UK CLL Forum guideline recommended alemtuzumab for use in patients without bulky lymphadenopathy (<5 cm), who were previously treated with alkylating agents and refractory to fludarabine. The evidence informing the UK CLL Forum recommendation was similar to the evidence contained in this report and was comprised of data from a smaller selection of single-arm studies. The German CLL Study Group determined that definitive recommendations could not be made regarding alemtuzumab use and indicated that further testing in clinical trials would be preferred. The Keating et al. guideline did not make explicit recommendations regarding the appropriateness of alemtuzumab use in CLL patients, but implied that alemtuzumab is appropriate in fludarabine-refractory patients. Keating et al. also stated that advanced age should not be a contraindication for alemtuzumab use.

The DSG considered the above recommendations to be based on low levels of evidence and, initially, was not convinced that these recommendations would inform the basis of a best clinical practice. Instead, the DSG initially concluded that potential benefits (response rates in a minority of patients, uncertain benefit in terms of response duration, overall survival, and quality of life) were offset by the potential for significant toxicity. Therefore, an initial recommendation was developed to indicate that there were insufficient data to support the routine use of alemtuzumab in patients with CLL. The DSG acknowledged the potential controversy that could result from issuing a "non–permissive" recommendation regarding alemtuzumab use and the potential implications such a recommendation might have for drug availability. The DSG was aware that its recommendations differed from those of other existing practice recommendations, including those published by ESMO and the UK CLL Forum.

The DSG was also aware that within the response data described from the literature reviewed were responses of a magnitude that reporting authors, and members of the DSG, considered to be clinically important. While the precise frequency of these responses were uncertain, and the best estimate was that they would be infrequent, the DSG acknowledged that an opportunity for such a response, even with substantial risks of toxicity, may be highly desired by some patients. The DSG attempted to reflect this sentiment by indicating that, after balancing the benefits and risks of treatment, certain patients may wish to consider a trial of therapy. While the DSG had concerns with issuing an unclear and potentially conflicting set of recommendations, it initially considered this option to represent the best available alternative and offered the following guidance: For patients with CLL, there is insufficient evidence to recommend the use of alemtuzumab outside of clinical trials. The DSG recognizes that, in highly selected cases, after thorough consideration of the risks and benefits, a trial of alemtuzumab might be considered. Section 3 of the original guideline document details the subsequent Practitioner Feedback and notes that responding clinicians were generally in agreement with the synthesis and interpretation of the available literature and the resulting recommendation. However, a small number of respondents commented on the lack of clarity associated with the recommendations. As a result, the DSG continued its consensus process in an effort to develop a clearer statement and issued a new set of recommendations. The redeveloped recommendation states, "Treatment with alemtuzumab is a reasonable option for patients with progressive and symptomatic CLL that is refractory to both alkylator-based and fludarabine-based regimens." In order to account for the continued concern about the level of evidence supporting this recommendation and the potential adverse risk-benefit profiles of this therapy, a detailed set of Qualifying Statements were also developed.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Internal Review

Following approval by Disease Site Group (DSG) members, the systematic review (Section 2 of the original guideline document) and recommendations (Section 1 of the original guideline document) were circulated to Ontario practitioners for feedback.

The recommendations were submitted with the systematic review to a sample of 95 hematologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on April 13, 2006, and a complete repeat mailing was sent thereafter.

Report Approval Panel

The final evidence-based series report was reviewed and approved by the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) in April 2006.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Treatment with alemtuzumab is a reasonable option for patients with progressive and symptomatic chronic lymphocytic leukemia (CLL) that is refractory to both alkylator-based and fludarabine-based regimens.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials, single-arm studies, and practice guidelines.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized controlled trial (RCT) evaluated alemtuzumab administered to consolidate a complete or partial response to first-line fludarabine-containing chemotherapy in patients with chronic lymphocytic leukemia (CLL). The study was stopped early due to the occurrence of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 grade III/IV infection-related toxicity in seven of the first 11 patients randomized to the alemtuzumab arm. Patients in that arm had a significantly improved progression-free-survival (PFS) compared to observation (no progression versus [vs.] a mean PFS of 24.7 months, p=0.036).
- Six single-arm studies evaluated disease response for alemtuzumab as a single agent in the treatment of patients with relapsed/refractory chronic lymphocytic leukemia post-fludarabine. The pooled overall response rate was 38% (complete response [CR] 6%, partial response [PR] 32%). Median time-

to-progression was reported in three of those trials and ranged from four to 10 months.

POTENTIAL HARMS

- One randomized controlled trial (RCT) evaluated alemtuzumab administered to consolidate a complete or partial response to first-line fludarabine-containing chemotherapy in patients with chronic lymphocytic leukemia (CLL). The study was stopped early due to the occurrence of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 grade III/IV infection-related toxicity in seven of the first 11 patients randomized to the alemtuzumab arm.
- Seventeen studies evaluated the toxicities associated with alemtuzumab as a single agent for the treatment of relapsed/refractory chronic lymphocytic leukemia:
    - Mild infusion-related side effects (e.g., grade I/II fever, rigors, vomiting, rash, dyspnea, and hypotension) were observed in most patients treated with intravenous alemtuzumab. Severe reactions (grade III/IV) were observed in up to 20% of patients treated with intravenous alemtuzumab; subcutaneous administration was rarely associated with severe infusion-related toxicity.
    - Thrombocytopenia and neutropenia (grade III/IV) were each observed in approximately one third of patients.
    - Infections were common (46% overall), often severe (18% grade III/IV), and included opportunistic, systemic viral, and invasive fungal diseases, despite antimicrobial prophylaxis. Cytomegalovirus (CMV) reactivation was commonly reported but effectively managed with adequate surveillance and treatment (usually intravenous ganciclovir); invasive CMV disease was rarely reported. Death due to infection occurred in approximately 4-5% of patients.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The evidence supporting treatment with alemtuzumab comes principally from case-series studies that evaluate disease response as the primary outcome measure. Patients should be informed that any possible beneficial effect of alemtuzumab on other outcome measures such as duration of response, quality of life, and overall survival are not supported in evidence and remain speculative at this time.
- Treatment with alemtuzumab is associated with significant and potentially serious adverse treatment-related toxicities. Patients must be carefully informed of the uncertain balance between potential risks of harm and the chance for benefit reported in studies. Given the current substantial uncertainty in this balance, patient preferences will likely play a large role in determining the appropriate treatment choice.
- Given the potential toxicities associated with alemtuzumab, and given the limited nature of the clinical trials testing its use in broad populations of patients with chronic lymphocytic leukemia (CLL), the use of alemtuzumab in patients with important co-morbidities may be associated with excessive risks.

- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Not Stated

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Fraser G, Smith CA, Imrie K, Meyer R, Hematology Disease Site Group. Alemtuzumab in chronic lymphocytic leukemia: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Jun 14. 32 p. (Evidence-based series; no. 6-16). [35 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Jun 14

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

None reported

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Alemtuzumab in chronic lymphocytic leukemia: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Jun 14. Various p.

(Practice guideline; no. 6-16). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 18, 2006. The information was verified by the guideline developer on August 23, 2006.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

Date Modified: 10/2/2006